Biomarkers in Severe Asthma

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KEYWORDS

• Severe asthma • Biomarker • Eosinophil • Periostin • Exhaled nitric oxide
• Endotype

KEY POINTS

- Asthma biomarkers can be broadly categorized as those that relate to type 2 inflammation and those that relate to other biological processes.
- Biomarkers of type 2 inflammation include sputum and blood eosinophils, exhaled nitric oxide levels, and serum periostin.
- In severe asthma, biomarkers are particularly useful in defining endotypes (ie, biologically related subtypes) and in predicting response to therapy.

INTRODUCTION

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] Biomarkers useful in respiratory disease can be obtained using several different types of clinical samples (**Box 1**). In this review, we restrict our discussion to biomarkers that can be measured in blood, sputum, or exhaled gas and those that are cellular, biochemical, or molecular in nature. There are several potential applications of biomarkers in the study and management of severe asthma (**Box 2**). Of these potential applications, significant advances have been made in biomarkers of endotypes (ie, biologically related subtypes) of asthma and in those that are predictive of response to therapy. In particular, biomarkers of type 2 inflammation (defined as inflammation driven by the Th2-cytokines, interleukin [IL]-4, IL-5, and IL-13) have proven valuable for endotyping in asthma. Here we review the current state of knowledge with respect to biomarkers in severe asthma, stratifying them by those that relate to type 2 inflammation and those that do not.

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Box 1
Sample types of biomarker measurement in respiratory disease

- Bronchoscopic samples
- Induced sputum
- Blood
- Urine
- Exhaled gases

BIOMARKERS OF TYPE 2 INFLAMMATION

Sputum Eosinophils

Sputum eosinophils are obtained by sputum induction and are expressed as a percentage of inflammatory cells.[2] Upper limit of normal for sputum eosinophil differential is generally defined as approximately 1% to 2%,[2–4] with female gender and atopy associated with higher sputum eosinophil counts.[3] Sputum eosinophil count is increased in symptomatic individuals with asthma,[5] and elevated eosinophils can be found in 50% of corticosteroid-treated patients, and in 70% to 80% of corticosteroid-naive patients.[6] Sputum eosinophil count is elevated by allergen challenge and reduced by corticosteroids.[7,8] Studies of inhaled corticosteroid (ICS) reduction in patients with asthma show that an increase in sputum eosinophil count may be predictive of asthma exacerbation.[9–11]

Fractional Exhaled Nitric Oxide Concentration

Nitric oxide (NO) is synthesized by NO synthetases (NOSs).[12] Patients with asthma have high levels of NO in their exhaled breath, which is thought to be due to upregulation of inducible NOS (NOS2) in airway epithelial cells secondary to airway inflammation.[13] Chemiluminescence analyzers allow the measurement of NO concentration in gas phase.[14] A joint American Thoracic Society (ATS) and European Respiratory Society (ERS) guideline (last revised in 2005) recommends that fractional exhaled NO concentration (FeNO) in exhaled breath be expressed as parts per billion (ppb).[15] FeNO is elevated in asthma and decreased with inhaled steroids.[16] The distribution of FeNO value is skewed to the right with significant overlap between healthy controls and patients with asthma. Current smoking, atopy, and age influence the distribution of FeNO values.[17–22] The 2011 ATS clinical practice guideline on the interpretation of FeNO proposes cutoffs for clinical use of FeNO. It suggests that eosinophilic

Box 2
Potential applications of biomarkers in severe asthma

- Understanding the biology
- Diagnosis and screening
- Assessment of severity, control, or prognosis
- Identification of endotypes (biologically related subtypes of disease)
- Application in clinical trials and safety monitoring
  - Pharmacodynamic biomarkers
  - Predictive of response